

included arcus senilis, greying of the hair and wrist size. A statistically significant correlation between the occurrence of coronary heart disease and the presence of each of these traits was found to exist, although there did not appear to be any clear interdependence of these traits. The presence of arcus senilis before the age of 56 and large wrist size were found to appear with a frequency in the coronary group which made their presence statistically significant at the 5% level. The occurrence of moderate greying of the hair and of premature greying (before the age of 35) was found to be highly significant (at the 1% level) in the coronary group. Hypercholesterolemia was a common finding in coronary patients who demonstrated arcus senilis and greying of the hair. Since it is a matter of only a few minutes to assess clinically and record these physical characteristics in any given person, it is suggested that greater attention be made to these features in all physical examinations. A few small steps have been taken in recent years in attempts to detect coronary atherosclerosis prior to its clinical manifestation. A simple clinical approach is suggested which may further aid in this continuing search.

It must again be stressed that the present study confirms the validity of long-standing clinical impressions about physical makeup and coronary disease. Three physical characteristics were studied. Their

presence in any one person should give impetus to further investigation of that individual and should in no sense be considered proof of the presence of, or evidence that, coronary disease will inevitably ensue.

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## Pinworm Infestation in Children: The Problem and Its Treatment

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**A**MONGST the intestinal parasitic worms of man, *Enterobius vermicularis*, or pinworm or threadworm or seatworm, is the smallest and the parasite that causes the least intestinal lesions. In spite of this, it has been known for the longest time.

In the writings of Hippocrates, Galen and Aristotle, it is called the "hopper" or the "jumper", owing to its manner of moving by hops and jerks. It was accused of producing many diseases, real and imaginary. Linnaeus, the great taxonomist, classified it after quite thorough studies. He also described the life cycle; unfortunately he made several important errors which delayed the recognition of the real epidemiology of the disease for a long time.

### LIFE CYCLE

*Enterobius vermicularis* (Fig. 1) is a small white worm. The female is 9 to 12 mm. in length and has a streamlined diameter of 1 mm. when she is not pregnant; then, she becomes bloated and deformed by some 10,000 eggs, more or less. The male is smaller, 2 to 5 mm. in length, and his posterior part is shaped like a fish hook complete with a barb. This structure is quite common in male round-

worms. The pinworm's life cycle is used classically as the prototype of parasitic cycle in a single host.

The eggs, which normally are in the embryo stage when laid, are usually found around the anus of the human host. In some cases, they may be found a few inches away in any direction. Sometimes immature females come out on the anal margin too soon and may wander as far as the vagina before they are ready to lay their eggs. The external membrane of the egg is very adhesive, enabling the eggs to conglomerate and to fix themselves to the tissues of their host. Some authors believe that this fixation is assisted by a very adhesive and irritating fluid that is secreted by the female; this secretion partly explains the intense pruritus ani felt by the host at that time.

Sometimes, gravid females rupture or lay their eggs in the terminal part of the intestinal tract. The eggs are immature and usually die, because they cannot develop to the embryo stage in the new environment.

After the eggs are laid, the very primitive embryo is transformed to a vermiform embryo in a few hours if the atmosphere is humid and the temperature is not less than 30° C. or 86° F. These conditions exist around the anus. As soon as this trans-

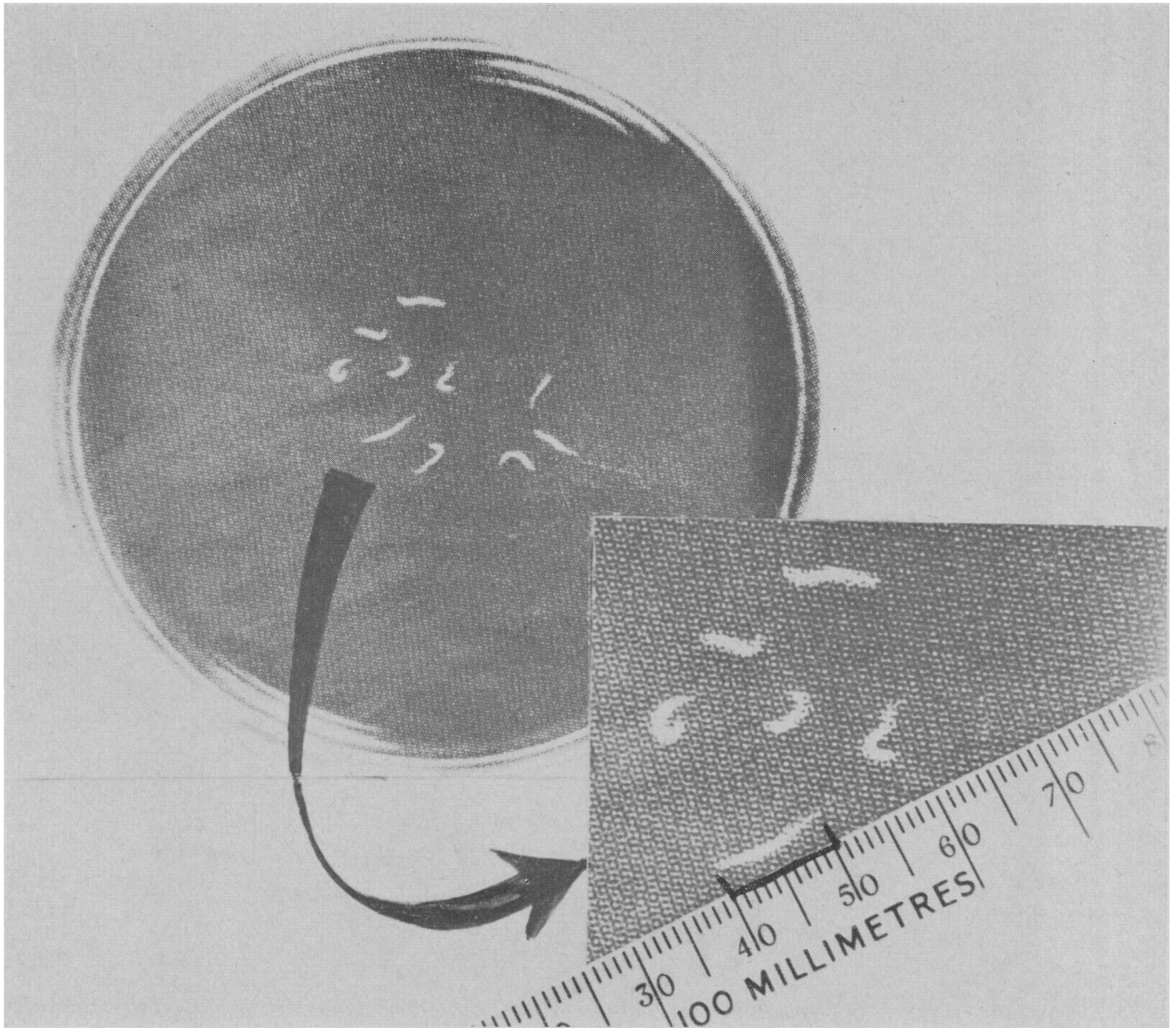


Fig. 1

formation has occurred, the egg is capable of continuing the infestation. This rapid change allows the re-infestation of the host that is characteristic of this condition; no other worm undergoes such rapid development. The pinworm embryo can survive up to 10 days under normal living conditions. Its membranes can stand exposure to air, light and dryness, if such exposure is not prolonged. The embryo can survive freezing for one or two days, and insecticides and poisons have little effect on it. However, the ideal conditions for survival and propagation are a humidity around 50% and a temperature not much above 70°-72° F.

#### MODES OF SPREAD

The eggs are transported to the mouth of the host in several ways (Fig. 2). Frequently the fingernails pick up the embryos from the peri-anal region during scratching, which is almost an automatic response to the pruritus that accompanies the laying of the egg. Examination of infested children showed embryos under the fingernails in more than 60% of cases. The eggs, once swallowed, are carried to

the duodenum, where the duodenal fluid softens the membranes, liberating the embryos. At this time they measure about 1/10 mm. The immature worms make their way to the terminal part of the small intestine or to the cecum, moulting a few times along the way. They mature in 14 days and copulate immediately. The males die soon after. The females stay in the cecum and the appendix for a short time, and then pass to the rectum. During the passage the eggs grow and the primitive embryos are formed. They are then ready to lay their eggs, but before doing so they wait for optimum conditions, which are attained when the host is under his blankets and resting quietly. They pass the ano-rectal junction, move about for a few centimetres and lay their eggs. This completes the cycle. Its total duration is from four to six weeks, and coincides with the cyclic episodes of pruritus in affected persons.

Infestation can also occur through the inhalation of dust that has been contaminated with eggs at the time of bed-making, dusting and sweeping. The eggs have been found disseminated widely

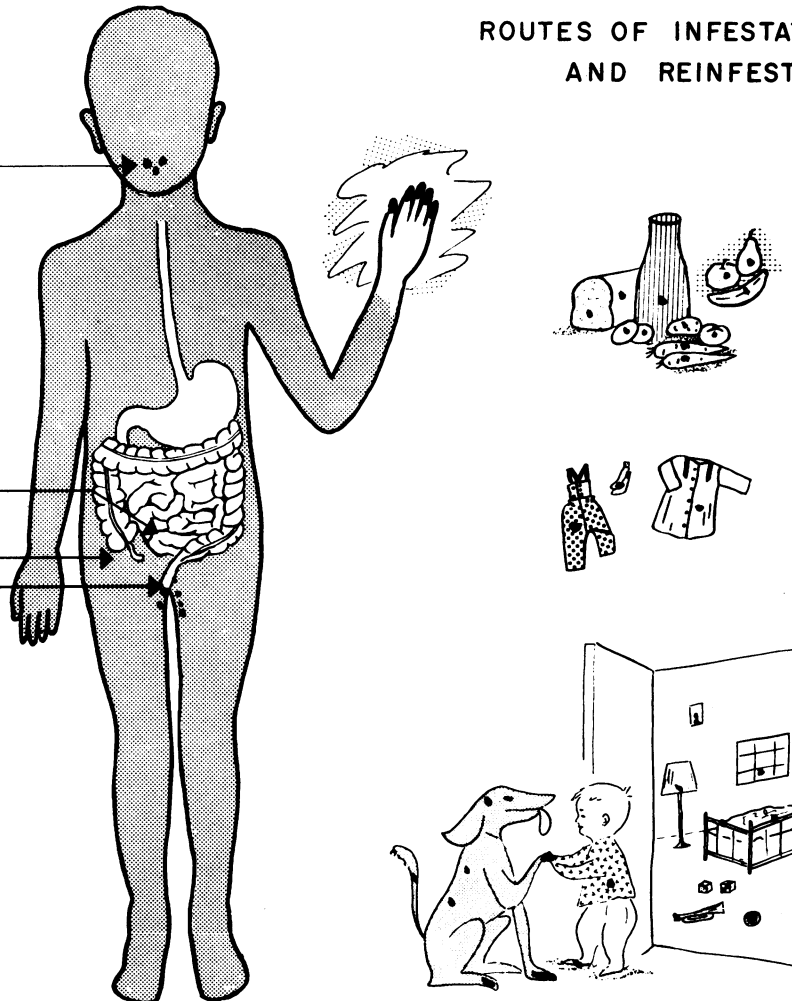
LIFE CYCLE OF  
ENTEROBIUS  
VERMICULARISInfestation and  
reinfestationFecundation  
Death of the maleHabitat  
Egg laying and  
death of the  
femaleROUTES OF INFESTATION  
AND REINFESTATION

Fig. 2

in the homes of infested persons, even on light fixtures and on the hairs of dogs and cats. In a survey of infested homes 221 of 241 specimens of dust were positive.

Another frequent route of infestation is on food and utensils contaminated by unclean hands. Finally, direct transfer may occur from person to person; this happens frequently among children or from infested children to the adult who is caring for them. Less frequently, an infested adult will contaminate the children under his or her care.

## INCIDENCE

The problem of oxyuriasis has a clinical importance beyond its symptomatology, because of its high frequency. Any physician who has interested himself in this problem is convinced that it is very frequent.<sup>1</sup> Many surveys have shown up to 50% positive cases among school children. Some authors, working in crowded areas and among low-income groups, report rates up to 90%.<sup>2</sup> In 1947 it was estimated that there were about 209,000,000 cases in the world.<sup>3</sup> It is well known that the incidence is higher in children than in adults and higher in children of school age than in the pre-school age group. Institutional life increases the incidence,

while rural life decreases it. All these variations are secondary to the possible frequency of contacts with infested persons. The only exception to this rule is that the incidence in Negroes is less than in white persons, although the former live in more crowded surroundings, at least in the low-income group. Cram's report<sup>4</sup> showed a rate of 41.5% in whites and 12.9% in Negroes. This has been confirmed by Brady<sup>5</sup> and Avery.<sup>6</sup>

At Sainte-Justice Hospital, repeated surveys have shown an incidence which varies from 40% to 60% in the school age group to less than 30% in the pre-school group and less than 20% in the country children. There were no Negroes in our surveys. In general, the rate in the high-income group was one-third to one-half of that for the corresponding low-income group.

In studies done among the siblings and parents of these cases, an incidence of 60 to 80% was found in the children and around 30% in the adults. In a similar study of contacts, Cram<sup>4</sup> reported 72% in children and 36% in adults. In the Negroes, the incidence was 51% and 7%, respectively. This familial incidence shows the absolute necessity of treating all the members of the family as soon as a single case is diagnosed.

All are in agreement that a large percentage of cases are asymptomatic and very often the discovery of the parasites is the result of a routine test or of a survey in the family of a known case. This asymptomatic state facilitates the spread of the infestation.

#### SYMPTOMS AND SIGNS

However, this condition has definite signs and symptoms. Pruritus ani, which may be mild to very severe, is the most frequent complaint. The pruritus recurs at regular intervals; this is not surprising, when one knows the egg laying habits of the worm. It comes at night, usually from one-half to one hour after the patient has retired. This coincides with the exit of the females and their movements about the peri-anal region. The egg-laying is accompanied by local irritation and inflammation that may be exaggerated by the usual scratching to the point of secondary lesions and infection. In chronic cases, there is frequently a transformation in eczema-like lesions which, being itchy in their own right, complete the vicious circle. Some authors believe that the initial inflammatory lesion is an allergic response to the female secretions or to the gluey outer membrane of the eggs. Many physicians accept anal itching in children as a specific sign of oxyuriasis. This has been shown to be true in over 80% of unselected cases of anal itching.<sup>1</sup>

Another very frequent symptom is irritability, which is probably secondary to the itching and to the lack of restful sleep. Initially, it is manifested by constant movement during the night, and then by insomnia, changes in disposition, loss of weight, and loss of appetite. This pattern can progress to a chronic emotional problem.

Pinworms have been accused of causing appendicitis in children; pathologists have devoted a lot of time to the study of this possibility. Of 14 reports, seven favour the direct or indirect action of the worm on the appendix. Many pathologists, among them Duran-Jorda,<sup>7</sup> who has found pinworms in 7.5% of 691 appendices, believe that the worm penetrates the mucosa and gives rise to pain without causing any pathological lesions. An equal number believe that the pinworms have nothing to do with appendicitis or that if they do, it must

be extremely rare. This opinion is supported by Gordon<sup>8</sup> in a survey of over 26,000 appendices. In our hospital, out of a total of 1804 appendices in the period 1956-58, pinworms were found in 197 cases.<sup>9</sup> Our pathologist believes that they are there in passing and do not take part in any inflammatory reactions; on the contrary, they are repelled by any pus formation.

Other symptoms to which lay people in general attach great value are nose scratching, teeth gnashing, fingernail chewing, nightmares, inattention in school or at home, and agitation; these are quite inconstant and when they exist, are secondary to the irritability already mentioned.

In the young girl, pinworms enter the genital tract in approximately 20% of cases. They may cause itching, which is rarely complicated by vaginitis and masturbation. Salpingitis and peritonitis are even rarer. Occasionally, in both sexes, there are well-substantiated reports of urinary frequency, bed-wetting and masturbation. This is thought to be a reflex action, secondary to the perianal itching.

#### TREATMENT

Many forms of treatment for pinworms have been suggested and used throughout the centuries. Some of these (Table I) now seem quite fantastic; others are still used, though they are not very effective. The blueberry cure reported by Nyberg consisted in feeding the child a pint of fresh blueberries four times in the first day, then once a day for the next six days. Garlic has been used either by mouth at the rate of a few buds every one to three hours for 10 to 14 days or in an enema at a rate of 1½ to 1 lb. per day, for 10 to 14 days. The rationale of this treatment was that the pinworms were repelled by the smell of garlic. This is not a very expensive treatment but is ineffective, as shown by Bumbalo, Gustina and Oleksiak,<sup>10</sup> who found a cure rate of 7%. The salt pork cure consisted in putting cubes of salt pork into the rectum every night for a prolonged period. When the cubes were withdrawn in the morning, they were covered with worms. The continuous purgation plan was based on the fact that the pinworms usually float around the intestinal lumen and it was hoped to float them out of the body. However, this treatment, which was kept up for at least seven days, resulted in a

TABLE I.—METHODS OF TREATMENT

<i>Historic</i>	<i>Recent</i>
1. <i>Fantastic</i> (a) Blueberry cure (b) Garlic cure (c) Salt pork cure (d) Continuous purgations	3. <i>Useful</i> —Cure rate 85 ± % (a) Gentian violet (b) Oxytetracycline (c) Piperazine
2. <i>Useless</i> —Cure rate 50 ± % (a) General hygienic measures alone (b) Thymol (c) Bismuth carbonate (d) Santonine (e) Calomel (f) Enemas and purgations (g) Ointments	4. <i>Very good</i> —cure rate 96% - 100% (a) Pyrvinium chloride (b) Dithiazanine
	5. <i>Ideal</i> —Cure rate 100% Pyrvinium pamoate

tremendous loss of weight and it may have killed a few patients.

The treatments in the second group in Table I were never very effective. Some were toxic and all were prolonged and quite disagreeable to the patient. The only exception is in a recent report by Jenkins,<sup>11</sup> who applied zinc oxide ointment liberally to the peri-anal region, four times a day for 21 days; he was able to report a cure rate of 80%.

Before examining improved forms of treatment that have been developed for pinworm infestation in recent years, the criteria for an ideal form of treatment are outlined.

Firstly, the treatment should be effective in more than 95% of cases; the closer a 100% cure rate is approached, the more ideal the treatment. Secondly, the treatment should be non-toxic, even when used in excess of therapeutic dosage. A large margin of safety is necessary so that repeated treatments, errors of prescription and accidental ingestion will not cause intoxication or possibly death. Thirdly, it should be easy to administer, so that family and institutional groups may be treated; this is the only sure way of eradicating the infestation. Fourthly, it must have a pleasant taste, so that it will be taken by every patient who needs it. This is not a serious matter in the hospital, but can be a very acute problem in some homes. Finally, the treatment should be available at reasonable cost, so that its use will be within the reach of large families or institutions.

The more recent forms of treatment (Table I), all quite effective, began with the use of gentian violet in 1940. This agent was given in two courses of eight days each with eight days' rest between. The pills were quite easy to swallow but sometimes a young child would chew a tablet and his clothes would be stained with the dye and he would dread thereafter the very disagreeable taste of the preparation. It was also somewhat toxic and its use was contraindicated in several diseases and in pregnancy. Oxytetracycline was introduced in 1952; 14 days of treatment were required and it caused proctitis in some individuals. Its cost was prohibitive. Piperazine was used in 1953, initially as the citrate salt. It had no undesirable side effects and its cost was reasonable, but it had to be given for two periods of one week with one week's rest, or for 14 days in a row. After a few years, the one-week schedule of treatment at a slightly higher dosage was used. Then it was used in a dosage of 3 g. for three days with 90.6% cures and 3 g. for two days with 86.2% cures.<sup>12</sup> In 1960 White and Scopes<sup>13</sup> reported the use of a modified piperazine preparation in a single dose of 3 to 4 g. with a 97% cure rate. There was a 10-15% incidence of abdominal complaints that included marked vomiting and frank diarrhea.

Many other preparations were tried out about that time. They included phenothiazine, promethazine, pyrazinazine, p-amino-benzylphenylcarbamate (Diphenan), Egressin, Lubisan and a few others.

They were abandoned because they were too toxic or because their cure rate was inferior to that of the agents in Group 3.

From 1953, pyrvinium chloride\* has been used at Sainte-Justine hospital and our results were reported in 1956.<sup>14</sup>

Since 1957, dithiazanine iodide has been used for the treatment of many helminthic infestations; it was shown to be effective. This agent is given for five days, and it had few side effects, except for some gastrointestinal irritation that was so severe that this product is no longer in use.

In 1958, a pamoate salt of pyrvinium,† was tried in pinworm infestation and a cure rate of 100% was obtained.

#### RESULTS OF TREATMENT

Work with the two pyrvinium preparations and the results obtained will be discussed in greater detail, since the pamoate form seems to approximate the criteria of an ideal treatment more closely than other therapeutic agents.

These two products belong to the group of the cyanine dyes. The chloride form was studied first, and the results obtained with it were very good (Table II). Other studies done in the United States and in Europe agreed with our results, the cure rate ranging from 96 to 100%.<sup>2, 15</sup> The treatment is simple enough, one dose per day for eight days. There were no signs of renal or hepatic toxicity and the taste was very acceptable to the children, but a few adults found it too cloying. In our series, two patients had negative results; one cellulose ("Scotch") tape test was positive for pinworms three days after the end of treatment, though subsequent "Scotch" tape tests were negative. We know now that this can happen in successful cases, but at that time we interpreted this as meaning failure of treatment and retreated these cases immediately.

Although pyrvinium chloride was clinically non-toxic and had a large margin of safety, animal research showed that the pamoate derivative was less than one-tenth as toxic and could be tolerated at very high dosage for a long period of time. This was confirmed recently in this hospital when a child who had swallowed 20 times the therapeutic dose was brought in; he showed no toxic effects.

TABLE II.—RESULTS OF TREATMENT

<i>Pyrvinium chloride</i>	
1½ mg./kg./day—8 days	150 cases—cure rate 98.6%
<i>Pyrvinium pamoate suspension</i>	
1½ mg./kg./day—8 days	37 cases—cure rate 100%
2-3 mg./kg./day—3 days	10 cases—cure rate 100%
5 mg./kg.—1 dose	61 cases—cure rate 100%
<i>Pyrvinium pamoate tablets</i>	
5 mg./kg.—1 dose	77 cases—cure rate 100%
	25 hospitalized patients
	38 in two institutions
	14 in two families

\*Supplied by Parke, Davis & Co. as POM 22—Poquil.

†Supplied by Park, Davis & Co. as Vanquin.

Clinically, the pamoate form has shown itself to be even more effective than the chloride form. Initially, it was used on the same dosage schedule, but when the "Scotch" tape tests were noted to be negative before the end of the treatment, a three-day schedule of treatment was tried at a slightly higher dosage, then a one-day treatment at 5 mg. per kg. With all three courses, the results were uniformly good.

There were a few patients who had a positive "Scotch" tape test between the second and the sixth day after treatment. However, controls were all negative between the 13th and 17th day without re-treatment. This has also been reported by Biguet,<sup>2</sup> who found a 100% cure rate with the one day treatment, as did Bumbalo, Plummer and Warner,<sup>16</sup> and others.<sup>15</sup> The tablets were used in a single dose of 5 mg. per kg. and a 100% cure rate was again obtained.

After this, family groups and institutions were treated; in both cases, there were no problems.

These results were obtained even though all the customary hygienic measures and associated treatments were eliminated. These measures were excluded because the true efficacy of the product was being evaluated, and not the sum of the efficacies of different products or techniques.

There were no clinical or laboratory signs of toxicity. Initially, the blood and the urine were examined for at least three months after treatment and there were no toxic changes. Eosinophilia was sometimes very marked, reaching 20 to 25% for a few days after treatment. This was probably due to an allergic response to the decomposition products of the worms.

The three forms of the pyrvinium preparation were very acceptable. Only one patient vomited the chloride form; of 2000 doses, only 9 were refused and the same patients took it afterwards without difficulty. The pamoate suspension was well accepted. Only two patients vomited and one was an habitual vomiter. Four adults who had to take seven to ten teaspoonfuls found it too cloying. With the tablets, there has been no problem.

Initially the taste of the product was tested in more than one hundred children, from prematures up to adolescents. It was uniformly well accepted.

The only disadvantage of the pamoate form in the one-dose treatment schedule is that in some cases the stools turn dark red. At first, this was mistaken for blood, a sign of intestinal irritation secondary to the product. It was soon evident clinically that it was not blood; this was confirmed by laboratory tests. We now know that this is only the surplus dye that is eliminated with the stools; there is no absorption through the intestinal wall or at most a very slight amount.

In addition to the patients reported in the controlled series (Table II), five to six times that number have been treated in our hospital with the same good results, namely acceptability by the patients and absence of toxicity.

TABLE III.—PRIMARY PATHOLOGY RESPONSIBLE FOR HOSPITALIZATION IN SOME CASES

Angioneurotic edema . . . . .	1	Eczema . . . . .	2
Asthma . . . . .	3	Glomerulonephritis . . . . .	3
Bronchopneumonia . . . . .	2	Infectious hepatitis . . . . .	5
Collagen disease . . . . .	1	Pneumonia . . . . .	1
Cystitis . . . . .	1	Pyelonephritis . . . . .	1
Diabetes . . . . .	7	Rheumatic fever . . . . .	4

There are no known clinical contraindications to the use of pyrvinium pamoate. After one is familiar with the product, it can be used when needed, irrespective of the primary pathology. In patients with renal or hepatic damage (Table III), it did not modify or aggravate the symptoms. It also seems to have no effect on allergic syndromes.

### CONCLUSIONS

In conclusion, one must remember that, owing to their particular life cycle, pinworms are hard to eradicate in a family and that it is hopeless to treat positive cases only.

Ideally, not only should the entire family group be treated, but any and all frequent contacts, especially those of school age who are responsible for so many cases of cross-infestation. For the same reasons, everybody in institutions should be treated at the same time.

Finally, more thought should be given to preventive treatment with pyrvinium pamoate. It has been shown to be effective and it is probable that its use will become more frequent, especially in families and institutions where there is a large population of school age children.

### SUMMARY

The problem of pinworm infestation has been discussed. Historic and current methods of treatment have been reviewed. The results obtained at Sainte-Justine Hospital have been presented. Pyrvinium pamoate (Vanquin) has been found to be the treatment of choice. It was well accepted, no toxic effects were found and a cure rate of 100% was obtained.

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### RÉSUMÉ

Le problème de l'oxyurose a été discuté. Les méthodes de traitement, anciennes et actuelles, ont été exposées. Les résultats obtenus à l'Hôpital Sainte-Justine ont été présentés. Le pamoate de pyrvinium (Vanquin) s'est révélé le meilleur traitement. Le produit est bien accepté, aucun effet toxique a été noté et un taux de guérison de 100% a été obtenu.